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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,453	12/19/2005	Mehmet Toner	50254/005002	8260
21559	7590	05/30/2008	EXAMINER	
CLARK & ELBING LLP 101 FEDERAL STREET BOSTON, MA 02110			WARE, DEBORAH K	
			ART UNIT	PAPER NUMBER
			1651	
			NOTIFICATION DATE	DELIVERY MODE
			05/30/2008	ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

<b>Office Action Summary</b>	<b>Application No.</b> 10/529,453	<b>Applicant(s)</b> TONER ET AL.	
	<b>Examiner</b> DEBBIE K. WARE	<b>Art Unit</b> 1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 31 January 2008.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 16, 17, 24, 25, 27, 44-46, 48-50, 70-89 and 117-130 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 16-17, 24-25, 27, 44-46, 48-50, 70-89, and 117-130 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>1/31/08</u> . | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

Claims 16-17, 24-25, 27, 44-46, 48-50, 70-89, and 117-130 are pending.

#### ***Response to Amendment***

The extension of time, declaration and amendment filed January 31, 2008, have been received and entered. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

#### ***Election/Restriction Withdrawn***

Applicant's amendments filed April 16, 2007, remove the requirement for restriction because all of the claims have been changed to the elected invention of record. Hence the restriction requirement has been removed because all claims are drawn to the same invention.

Claims 16-17, 24-25, 27, 44-46, 48-50, 70-89, and 117-130 are reconsidered on the merits.

#### ***Information Disclosure Statement***

The information disclosure statement (IDS) submitted on January 31, 2008, was received. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

#### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 45, 70-89, and 119-130 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 45 is rendered vague and indefinite because it is unclear which step of claim 44 the obstacles are coated with a binding moiety that binds to the surface, thus, it is suggested to insert at line 1, after “said obstacles” —of step (ii)— .

Claims 70-80 are rendered vague and indefinite for the releasing step wherein the same is suggested as set forth above for claim 45.

Claims 76 and 85 are further rendered vague and indefinite for not providing antecedent basis for the cell types recited at line 2 of claim 76 and line 1 of claim 85 and it is suggested at line 1 of claim 76 to insert after “first type” —of cell—and the same insert at line 1 for claim 85.

Claim 77 is also further rendered vague and indefinite for not adequately defining the identifying step as a further step of claim 70 and it is suggested at line 1 of claim 77 to inserted after “claim 70,” —further comprising—.

Claim 81 is also rendered vague and indefinite for the staining step wherein it is unclear which step of claim 44 is being referred back to, and hence, it is suggested to insert after “staining cells bound to said obstacles” —of step (ii)— .

Also it is suggested to include —further comprising—as an insert after “claim 81,” and “claim 121,” in claims 86 and 130, respectively, for the same reasons as discussed above for claim 77.

Claim 89 lacks antecedent basis for the recitation of “second type” at line 1.

Claim 119 lacks antecedent basis for the recitation of “one direction” at line 3.

Claim 121 is rendered vague and indefinite for failing to recite clear and distinct process steps and it is suggested to change “first sample” at line 5 to “blood sample” and to further include the language as an insert after first occurrence of “sample” --and releasing bound cells from said obstacles-- at line 5 of claim 121.

Claim 122 lacks antecedent basis for the recitation of “one direction” at line 3.

Claim 129 also lacks antecedent basis for the recitation of “said first type” at line 1. and hence it is suggested to insert after it the terminology “of cell--”.

### ***Response to Arguments***

Applicants’ arguments presented January 31, 2008, have been deemed persuasive with respect to the previous rejection and it is acknowledged that Applicants did not choose to provide the language as previously suggested in the last Office action.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

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were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 16-17, 24-25, 27, 44-46, 48-50, 70-89, and 117-130 are rejected under 35 U.S.C. 103(a) as obvious over Spence et al (US2002/0005354A1), cited on previously enclosed PTO-892 Form, in view of newly cited Singhvi et al (US 7067306) and previously cited Chou et al, all cited on enclosed and previously enclosed PTO-892 Forms.

Claims are drawn to method of producing a cell population enriched in a first cell type comprising subjecting blood sample to separation comprising contact with a microfluidic channel comprising obstacles so that smaller cells are directed in one direction and larger cells are directed in another second direction and separation comprising contact with the device to produce an enriched cell population.

Spence et al teach a method of producing a cell population enriched in a first cell type, note page 3, column 1, line 4, and page 5, column 2, [0054], line 15 and page 8, column 1, [0078] lines 1-2 and column 2, [0082], all lines. The microfluidic device is disclosed.

Singhvi et al teach a device containing obstacles (cytophilic islands) separated by gaps (cytophobic regions) for adhering cells by binding the cells preferentially to the islands. See the abstract and column 1, lines 30-40.

Chou et al teach the obstacles to be pillars, note figure 1, of page 12, wherein support pillars are used to support the microfluidic device channels.

The claims differ from Spence in that obstacles as pillars are not clearly disclosed for preferential binding of cells thereto.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the teachings of Spence et al, Singhvi et al and Chou et al, as cited above to provide for a method for producing an enriched cell population via cell-based size separation or cell-binding separation using a microfluidic device having obstacles as pillars as clearly disclosed by the combination of Spence et al, Singhvi et al and Chou et al, respectively. Spence et al do teach that cells so separated are separated according to predetermined characteristics of which size based separation; and/or cell binding based separation is/are obvious modification(s) of the cited prior art. An obstacle at which separation occurs is noted in Figure 6 of Spence. The secondary reference, Singhvi et al, clearly suggests that obstacles in a device can be used for binding cells thereto. Also the secondary reference of Chou et al clearly teach the obstacle to include raised pillars as required by the instant claims. Furthermore, the cells, such as red blood cells, which are disclosed and so being separated can flow in different directions as they are separated.

Further, the blood cells can be human which includes fetal blood cells. The percentage of cells which can selectively bind can be accurately controlled by the microprocessor disclosed to be on the chip of the reference. Also the two dimensional array is disclosed by the reference since there is more than one channel. Further, the

direction is disclosed to be reversible and so the property of preferential reversible binding is an intrinsic feature of the disclosed chip.

In addition, the reference discloses a window at page 8, [0081], line 5, which can intrinsically function to serve as a field for actuating preferential binding as necessary. It would have been obvious to design the program of the disclosed device to provide for 60% of the first type and 70% of cells of the second type, and further to provide for a binding moiety to control flow in a two-dimensional array and to separate the cells based upon size and/or their binding capabilities. Also to select for a fetal cell is clearly within the guidance of the description of the cited reference. Each of the claimed features are either taught or suggested by the above cited prior art combination. The claims are suggested if not disclosed by the cited prior art and are prima facie obvious over the cited prior art.

### ***Response to Arguments***

Applicant's arguments and declaration filed January 31, 2008, have been fully considered but they are not persuasive in light of the newly discovered reference as applied above in combination with the previously cited prior art. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The deficiencies of Spence et al and Chou et al are believed by the Examiner to be resolved by the addition of Singhvi et al because they teach or at least suggest that

obstacles in devices can be used to bind cells. To provide for this separate technique in the art to combine with cell size based exclusion is an obvious modification of the cited prior art. To provide for obstacles in a device to enrich cell populations is an obvious step and one of skill based upon the teachings of the cited prior art would have expected successful results. Applicants' Declaration filed by Dr. Kapur under 37 CFR 1.132 is persuasive with respect to the prior art rejection, however, the Singhvi et al reference does teach preferential binding in a device, of which can include as an obvious modification of the cited prior art a microfluidic device.

One of skill would have been motivated to combine techniques to enhance cell population concentration and to achieve improved results. The teachings that Spence and Chou teach that the pillars disclosed therein are used to support and prevent collapse of the channels is noted, however, in view of the teachings of Singhvi et al these supports can be easily coated as desired for cell binding to enhance cell population studies. Cell binding and cell size based separation are well known and recognized techniques in the art as are the microfluidic device for use with red blood cells. These devices are well known and widely used for separating red blood cells according to size and other predetermined characteristics as desired. The claims are rendered prima facie obvious over the newly cited prior art combination.

The claims are suggested by the cited prior art and deemed prima facie obvious over the prior art.

All claims fail to be patentably distinguishable over the state of the art discussed above and cited on the enclosed and previously enclosed PTO-892 and/or PTO-1449. Therefore, the claims are properly rejected.

The remaining references listed on the enclosed PTO-892 and/or PTO-1449 are cited to further show the state of the art.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah K. Ware whose telephone number is 571-272-0924. The examiner can normally be reached on 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/DKW/  
Deborah K. Ware  
May 10, 2008

/David M. Naff/  
Primary Examiner, Art Unit 1657